Title	A U-Turn in the Asymmetric Appel Reaction: Stereospecific Reduction of Diastereomerically Enriched Alkoxyphosphonium Salts Allows the Asymmetric Synthesis of P-Stereogenic Phosphanes and Phosphane Boranes
Authors(s)	Rajendran, Kamalraj V., Kudavalli, Jaya S., Dunne, Katherine S., Gilheany, Declan G.
Publication date	2012-04-05
Publication information	Rajendran, Kamalraj V., Jaya S. Kudavalli, Katherine S. Dunne, and Declan G. Gilheany. “A U-Turn in the Asymmetric Appel Reaction: Stereospecific Reduction of Diastereomerically Enriched Alkoxyphosphonium Salts Allows the Asymmetric Synthesis of P-Stereogenic Phosphanes and Phosphane Boranes.” Wiley, April 5, 2012. https://doi.org/10.1002/ejoc.201200285.
Publisher	Wiley
Item record/more information	http://hdl.handle.net/10197/4936
Publisher's statement	This is the author's version of the following article: Rajendran, K. V., Kudavalli, J. S., Dunne, K. S. and Gilheany, D. G. (2012), A U-Turn in the Asymmetric Appel Reaction: Stereospecific Reduction of Diastereomerically Enriched Alkoxyphosphonium Salts Allows the Asymmetric Synthesis of P-Stereogenic Phosphanes and Phosphane Boranes. Eur. J. Org. Chem., 2012: 2720–2723 which has been published in final form at http://dx.doi.org/10.1002/10.1002/ejoc.201200285
Publisher's version (DOI)	10.1002/ejoc.201200285

DOI: 10.1002/ejoc.200((will be filled in by the editorial staff))

A U-turn in the Asymmetric Appel Reaction: Stereospecific Reduction of Diastereomerically Enriched Alkoxyphosphonium Salts allows the Asymmetric Synthesis of *P*-Stereogenic Phosphines and Phosphine Boranes

Kamalraj V. Rajendran, Jaya S. Kudavalli, Katherine S. Dunne and Declan G. Gilheany*[a]

Keywords: Phosphine / Phosphine borane / *P*-stereogenic / *P*-chiral / *P*-chirogenic / Asymmetric synthesis / Appel conditions / Alkoxyphosphonium salts.

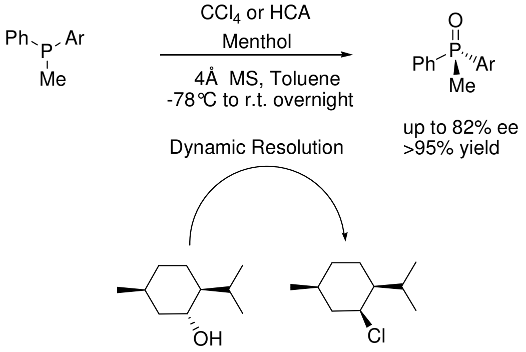
An efficient one pot synthesis has been developed of enantioenriched *P*-stereogenic phosphines and phosphine boranes from the corresponding racemic phosphines in excellent yield under asymmetric Appel conditions. The chiral auxiliary (menthol) can also be recovered unchanged. The simple and efficient protocol significantly expands the scope of our asymmetric Appel process. The crucial step in the preparation involves stereospecific reduction of intermediate diastereomeric alkoxyphosphonium salts, which are obtained by reacting phosphine, hexachloroacetone, and menthol. Thereby, reaction with $LiAlH_4$ or $NaBH_4$ gives the corresponding phosphines or phosphine boranes respectively.

Introduction

Asymmetric catalysis has become an essential strategy for carrying out various asymmetric transformations[1] and enantioenriched phosphine ligands are common catalyst components.[1a-c] Thus significant effort has been expended in the design, synthesis, and testing of new enantiomerically pure phosphines for various synthetic purposes.[2] An important part of that effort has seen the development of a large number of methodologies for the synthesis of *P*-stereogenic phosphines[3] and a large number of such enantiomerically pure phosphine ligands have been reported in the literature.[1c,4,5] Some of these methods are very effective, but each of them has its own limitations and it is true to say that a general procedure for the synthesis of *P*-stereogenic phosphines has not been developed thus far. In seeking a general solution to this problem, we developed[6] a dynamic kinetic resolution (DKR) in the oxidation of phosphines under Appel[7] reaction conditions (Scheme 1). The purpose of this communication is to disclose a significant improvement to this methodology that allows the expansion of the range of compounds synthesised to include enantioenriched tertiary *P*-stereogenic phosphines or their protected phosphine boranes.

Results and Discussion

Our asymmetric Appel methodology (Scheme 1) utilises hexachloroacetone (HCA) as a chlorine source and a chiral alcohol such as menthol to make enantioenriched phosphine oxides from racemic phosphines. Although this is an efficient way to make *P*-stereogenic phosphorus compounds, it suffers from some drawbacks, one of which is that a subsequent (and potentially problematic) stereospecific reduction of the product phosphine oxide [4d, 8] is required to obtain the target phosphine. Another drawback is that the menthol auxiliary is converted to the derived chloride making its reuse difficult.

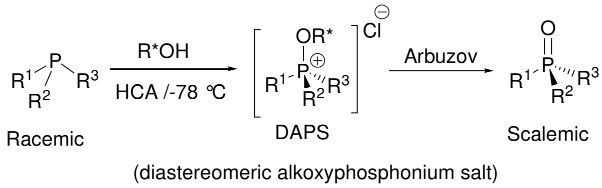


Scheme 1. DKR in oxidation under Appel conditions.

As part of our studies of this process with various alcohol/phosphine combinations, we observed, in the ^{31}P-NMR, an unequal pair of signals in the region δ 65-67 ppm. These were identified [6] as diastereomeric alkoxyphosphonium salts (**DAPS**), which undergo Arbuzov collapse to form the phosphine oxide (Scheme 2). Denton and co-workers have recently isolated and characterised similar alkoxyphosphonium salt intermediates in their catalytic Appel reactions.[9]

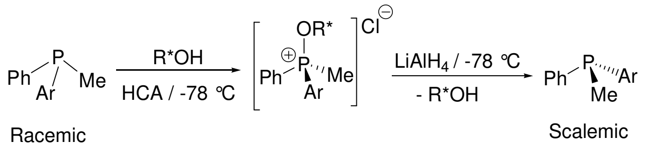
---

[a] Centre for Synthesis and Chemical Biology, School of Chemistry and Chemical Biology, University College Dublin, Belfield, Dublin 4, Ireland
E-mail: declan.gilheany@ucd.ie
Fax: +353-1-7162127
Supporting information for this article is available on the WWW under http://www.eurjoc.org/ or from the author.



Scheme 2. **DAPS** intermediates in the asymmetric Appel process.

In order to isolate a stable form of these intermediates we used (*R*)-BINOL as the alcohol in an Appel type reaction with methyl(phenyl)-*o*-tolylphosphine at -78 ˚C in dry toluene. On addition of HCA, a mixture of diastereomeric aryloxyphosphonium salts precipitated (Scheme 3; R*OH = (*R*)-BINOL). Because they are unable to undergo Arbusov collapse, these could be isolated and characterised (as the mixture) by ^{31}P-NMR, HRMS and elemental analysis (see supporting information for details). The salts were found to have been formed in a diastereomeric excess (de) of 46% (as measured by integration [10] of their ^{31}P signals at δ 74.7 and 76.6 ppm). The salts were then subjected to reduction using $LiAlH_4$, resulting in full conversion to enantioenriched methyl(phenyl)-*o*-tolylphosphine (Scheme 3). The enantiomeric excess of the phosphine was determined to be 46% (by CSP-HPLC analysis of the corresponding phosphine borane formed by treatment with BH_3.THF). This indicated that there had been no loss of stereochemical information during the reduction step. (*R*)-BINOL was also recovered.



Scheme 3. One pot generation and stereospecific reduction of **DAPS** using $LiAlH_4$.

We realised that this transformation might also be applied to the transient **DAPS** formed with menthol under Appel conditions, by application of the reducing agent before Arbuzov collapse to the phosphine oxide takes place. In such a way, the Appel reaction might effectively undergo a “U-turn”, re-forming phosphine but in enantiomerically enriched form, without the need for additional stereospecific reduction. Literature precedent suggests competing alcohol reduction is inhibited in the case of menthol.[11,12]

In initial studies, methyl(phenyl)-*o*-tolylphosphine underwent reaction with HCA and (-)-menthol in toluene at -78 ˚C to form **DAPS** (confirmed by ^{31}P NMR showing two peaks at δ 65.7 and δ 67.4 ppm; with a de of 80%). Ten minutes after the start of the reaction[13] the **DAPS** were reduced in the same pot by adding $LiAlH_4$ in THF to give the corresponding phosphine quantitatively. However, extensive optimisation of the reaction protocol was required in order to find conditions which did not result in erosion of isomeric excess (see supporting information for details). Finally we were able to obtain methyl(phenyl)-*o*-tolylphosphine in 79% ee from **DAPS** of 80% de. We applied this methodology to a variety of phosphine/alcohol (Chart 1) combinations with the results detailed in Table 1, again measuring the ee following subsequent conversion to the borane with borane-THF.

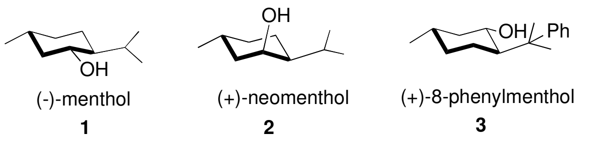


Chart 1. Chiral non-racemic alcohols used in Tables 1 and 2.

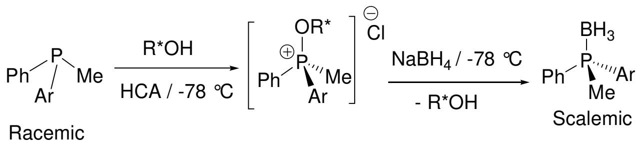
Table 1 also gives, for comparison, the analogous enantioselectivities of the phosphine oxide products obtained in the regular asymmetric Appel reaction of the same phosphines, reported in our previous work.[6] It can be seen that, mostly, these are the same, the exceptions being where there are notable changes in the alcohol (entry 6) or phosphine used (entries 10-12). We attribute these variations to the need for optimisation of the conditions in these cases.

Table 1. Enantiomeric excess of phosphines (ArPhMeP) prepared by treatment of diastereomerically enriched alkoxyphosphonium salts with $LiAlH_4$ according to Scheme 3.[a]

#	Ar	R*OH[b]	% ee[c] of phosphine (config.)	% ee of analogous oxide[d]
1	*o*-tolyl[e]	**1**	79 (*R*)	80
2	*o*-tolyl	***ent*-1**	-76 (*S*)	78
3	*o*-tolyl	**2**	-71 (*S*)	71
4	*o*-anisyl[e]	**1**	50 (*R*)	50
5	*o*-anisyl	***ent*-1**	-48 (*S*)	49
6	*o*-anisyl	**3**	64 (*R*)	77
7	*o*-biphenyl[e]	**1**	65 [f]	64
8	*o*-*tert*-butylphenyl[e]	**1**	60 [f]	57
9	*o*-trifluoromethylphenyl[e]	**1**	70 [f]	71
10	*o*-isopropylphenyl[e]	**1**	58 (*R*)	80
11	*o*-methyl-*p*-fluorophenyl	**1**	57 [f]	76
12	*o*,*p*-dimethylphenyl[e]	**1**	60 [f]	76

[a] Reaction conditions: phosphine (1.1 mmol), alcohol (1.32 mmol), HCA (1.1 mmol), $LiAlH_4$ (1.1 mmol), all at -78 ˚C, crude yields >95% (as determined by ^{31}P NMR); [b] see Chart 1; [c] measured following conversion to the borane with borane-THF, determined by CSP HPLC, a negative ee denotes that the major enantiomer was eluted second; absolute configurations determined as described in the SI; [d] ee of the analogous phosphine oxide formed when the DAPS was allowed to undergo Arbuzov collapse, from references [6]; [e] isolated yields >85%; [f] configuration not assigned.

At the same time that this work was in progress, we had been investigating the use of $NaBH_4$ as reductant for other phosphonium salts including enantioenriched alkoxy cases.[14] We had found that the phosphine borane could be produced directly in such reactions.[11] As much attention has been directed towards phosphine boranes in recent years,[3e,j,n, 15] we also studied this variant, Scheme 4, with various phosphine/alcohol combinations with the results shown in Table 2. In most cases the ees obtained are the same as those obtained in the $LiAlH_4$ reduction.



Scheme 4. One pot generation and stereospecific conversion of **DAPS** to phosphine borane using $NaBH_4$.

Table 2. Enantiomeric excess of phosphine boranes (ArPhMeP-BH_3) prepared by treatment of diastereomerically enriched alkoxyphosphonium salts with $NaBH_4$ according to Scheme 4.[a]

#	Ar	R*OH[b]	% ee[c] of *P*-borane (config.)	% ee of analogous oxide[b]
1	*o*-tolyl [e]	**1**	75 (*R*)	80
2	*o*-tolyl	***ent*-1**	-74 (*S*)	78
3	*o*-anisyl [e]	**1**	50 (*R*)	50
4	*o*-anisyl	***ent*-1**	-51 (*S*)	49
5	*o*-anisyl	**3**	63 (*R*)	77
6	*o*-biphenyl[e]	**1**	66 [f]	64
7	*o*-trifluoromethylphenyl[e]	**1**	71 [f]	71
8	*o*-isopropylphenyl[e]	**1**	40 (*R*)	80

[a] Reaction conditions: phosphine (1.1 mmol), alcohol (1.32 mmol), HCA (1.1 mmol), $NaBH_4$ (5.5 mmol), yields >95% (as determined by ^{31}P NMR); [b] see Chart 1; [c] Determined by CSP HPLC; a negative ee denotes that the major enantiomer was eluted second; absolute configurations determined as described in the SI; [d] ee of the analogous phosphine oxide formed when the DAPS was allowed to undergo Arbuzov collapse, from references [6]; [e] isolated yields >85%; [f] configuration not assigned.

The significance of the results in Tables 1 and 2 does not lie in the absolute degree of selectivity obtained. We have focussed mostly on the use of inexpensive menthol as the chiral auxiliary to show proof of principle that the asymmetric Appel process can be manipulated to produce scalemic phosphines or phosphine boranes in one pot from a racemic phosphine. Also, the selectivities are, in most cases, the same as previously seen in the regular asymmetric Appel process.[6] Thus we have significantly expanded the utility of our asymmetric Appel process. With this methodology in hand, we have embarked on an intensive study aimed at raising the degree of stereoselectivity in our process. In that context, an important point is that the chiral auxiliary can now be recovered intact in the present process, which allows us greater scope in our choice of chiral alcohols for our selectivity studies, knowing that they can be recovered at the end of the reaction.

Conclusions

In conclusion, we have achieved an unprecedented one-pot enantio-enrichment of racemic phosphines and we have demonstrated the one-pot conversion of racemic phosphines to enantioenriched phosphine boranes. Both methods rely on the interception of diastereomeric alkoxyphosphonium salts formed by dynamic resolution of racemic phosphines under asymmetric Appel reaction conditions. Further investigations into the scope of this reaction are underway.

Experimental Section

(A) Preparation and Pre-drying of Stock Solutions: Moisture was rigorously excluded in these experiments. Dry solvent used to make up stock solutions was obtained after processing through an Innovative Technology Inc. Pure Solv-400-3-MD solvent purification system (Grubb's still). The water content of the solvent and stock solutions was determined by Karl Fischer titration to be less than 5 ppm. The alcohols, phosphines and hexachloroacetone (HCA) used were dried thoroughly before preparing the stock solutions as follows. The individual alcohols (1.32 mmol.) were weighed into flame-dried and N_2-purged round-bottomed flasks and sufficient dry toluene (approx. 10 mL) added to dissolve the alcohol. The toluene was removed using a rotary evaporator to remove water *via* azeotrope. This process was repeated three times and then sufficient dry toluene was added to the alcohols under N_2 to make up solutions of the required concentration (0.132 M). Molecular sieves (4 Å), which were flame-dried until red hot, were added after cooling to flame-dried Young's flasks. The flasks were heated under vacuum with a heat gun focusing on the molecular sieves for two minutes each and then flushed with N_2. This was repeated twice. The Young's flask screw crown was removed under a good flow of N_2 and replaced with a rubber septum. While both vessels were under nitrogen the stock solutions were removed *via* syringe from the round-bottomed flasks and placed over the sieves in the Young's flasks and left overnight. For the HCA solution, molecular sieves (4 Å), which were flame-dried until red hot, were added to flame-dried Young's flasks. The flasks were heated under vacuum with a heat gun focusing on the molecular sieves for 2 minutes each and then flushed with N_2. This was repeated twice. The screw cap of the Young's flask was removed under a good flow of N_2 and replaced with rubber septa. Distilled HCA (1.1 mmol.) was weighed into the Young's flask and dry toluene was added to make up a solution of the required concentration (0.11 M) which was then left overnight. A similar procedure was followed to make up 0.11 M stock solutions of distilled phosphines in dry toluene.

(B) Optimised Procedure for $LiAlH_4$ Reduction with methyl(phenyl)-*o*-tolylphosphine as example.

A solution of methyl(phenyl)-*o*-tolylphosphine (10.0 mL, 0.11 M 1.1 mmol) in anhydrous toluene was placed in a dry flask under N_2. In a separate flask were placed dry toluene solutions of HCA (10.0 mL, 0.11 M, 1.1 mmol) and (-)-menthol (10.0 mL, 0.132 M, 1.32 mmol) also under N_2. Both flasks were cooled to -78 °C and allowed to stir at this temperature for 10 minutes. After this time the phosphine solution was added steadily *via* cannula over 2 minutes. The temperature was maintained for 10 mins, at which point the formation of the diastereomeric salts was confirmed by ^{31}P NMR (sampled as described in the SI) showing two peaks at δ 65.7 and δ 67.4 ppm. To the mixture was added $LiAlH_4$ solution (10.0 mL, 0.11 M in toluene, 1.1 mmol) dropwise at -78 °C. After the addition was complete the vessel was removed from the cooling bath and allowed to warm to room temperature. The reaction was stirred for a further 60 minutes, at which point the diastereomeric salts were shown to have been consumed and the phosphine formed (^{31}P NMR signal at δ -36.2 ppm). $BH_3 \cdot THF$ complex (0.75 mL of a 2.0 M solution in THF, 1.5 mmol) was added. ^{31}P NMR of the clear solution revealed one peak for the phosphine borane at δ 10.1 ppm. A portion of the reaction mixture was removed, concentrated under reduced pressure, diluted in HPLC mobile phase, filtered though a 0.2 µM Millipore Acrodisc and directly injected (10 µL) onto the HPLC system (see SI) for ee analysis. The remaining reaction mixture was diluted with EtOAc (15 mL) and water (10 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was passed through a column of basic alumina using degassed Et_2O. The solvent was removed under vacuum and column chromatography was carried out on silica gel (EtOAc, R_f 0.11) yielding the enantioenriched phosphine borane as a white solid (0.20 g, 96%, 79% ee (*R*)).

(C) Optimised Procedure for $NaBH_4$ Reduction with methyl(phenyl)-*o*-tolylphosphine as example.

Experimental procedure as per section **(B)** up to the analysis of diastereomeric salts by ^{31}P NMR. To the mixture was added $NaBH_4$ solution (11 mL of a 0.5 M solution in diglyme, 5.5 mmol) dropwise at -78 °C. After the addition was complete the vessel was removed from the cooling bath and allowed to warm to room temperature. The reaction was stirred for a further 60 minutes, at which point the diastereomeric salts were shown to have been consumed and the phosphine borane formed (^{31}P NMR signal at δ 10.1 ppm). Work up and analysis as per section (**B**) gave the enantioenriched phosphine borane as a white solid (0.19 g, 94%, 75% ee (*R*)).

Supporting Information (see footnote on the first page of this article):

Acknowledgments

We sincerely thank Science Foundation Ireland (SFI) for funding this research under grants 08/RFP/CHE1251 and 09/IN.1/B2627. We are also grateful to the Centre for Synthesis and Chemical Biology and the UCD School of Chemistry and Chemical Biology for access to their extensive analysis facilities.

---

[1] (a) I. Ojima, Ed.; *Catalytic Asymmetric Synthesis*, 3rd ed.; Wiley-VCH: New York **2010**; (b) X. Zhang, Ed. *Tetrahedron: Asymmetry* **2004**, *15*, 2099-2311, special issue. (c) K. V. L. Crepy, T. Imamoto, *Top. Curr. Chem.* **2003**, 1; (d) Seayad, J. List, B. *Org. Biomol. Chem.* **2005**, *3*, 719-724; (e) Connon, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3909-3912. (f) J. L. Methot, W. R. Roush, *Adv. Synth. Catal.* **2004**, *346*, 1035-1050.

[2] A. Börner, Ed. *Phosphorus Ligands in Asymmetric Catalysis*; Wiley-VCH: Weinheim, **2008**; Vols. I-III.

[3] Menthyl phosphinate route (a) O. Korpium, K. Mislow, *J. Am. Chem. Soc.* **1967**, *89*, 4784-4786; (b) B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, D. J. Weinkauff, *J. Am. Chem. Soc.* **1977**, *99*, 5946-5952; (c) T.Oshiki, T. Imamoto, *J. Am. Chem. Soc.* **1992**, *114*, 3975-3977; (d) D. Moraleda, D. Gatineau, L. Martin, G. Buono, *Chem. Commun.* **2008**, 3031-3033; (e) D. Gatineau, L. Laurent Giordano, G. Buono, *J. Am. Chem. Soc.* **2011**, 133, 10728-10731; (f) Q. Xu, C.-Q. Zhao, L.-B. Han, *J. Am. Chem. Soc.* **2008**, *130*, 12648-12655. Cyclic phosphoramidate route (g) S. Jugé, J. P. Genet, *Tetrahedron Lett.* **1989**, *30*, 2783-2786; (h) C. Darcel, J. Uziel, S. Jugé, in: *Phosphorus Ligands in Asymmetric Catalysis* (Ed.: A. Börner), Wiley-VCH, Weinheim, **2008**, vol. 3, p. 1211–1233; (i) T. Leon, A. Riera, X. Verdaguer, *J. Am. Chem. Soc.* **2011**, *133*, 5740-5743; (j) M. Revés, C. Ferrer, T. León, S. Doran, P. Etayo, A. Vidal-Ferran, A. Riera, X. Verdaguer, *Angew. Chem. Int. Ed.* **2010**, *49*, 9452-9455; Desymmetrisation: (k) A. R. Muci, K. R. Campos, D. A. Evans, *J. Am. Chem. Soc.* **1995**, *117*, 9075-9076; (l) A. Ohashi, S. I. Kikuchi, M. Yasutake, T. Imamoto, *Eur. J. Org. Chem.* **2002**, 2535-2546; (m) J. J. Gammon, V. H. Gessner, G. R. Barker, J. Granander, A. C. Whitwood, C. Strohmann, P. O'Brien, B. Kelly, *J. Am. Chem. Soc.* **2010**, *132*, 13922-13927; (n) J. Granander, F. Secci, S. J. Canipa, P. O'Brien, B. Kelly, *J. Org. Chem.* **2011**, 76, 4794-4799; Enzymatic resolution: (o) P. Kielbasinski, J. Omelanczuk, M. Mikolajczyk, *Tetrahedron: Asymmetry* **1998**, *9*, 3283-3287; Dynamic resolution: (p) B. Wolfe, T. Livinghouse, *J. Am. Chem. Soc.* **1998**, *120*, 5116-5117; (q) H. Heath, B. Wolfe, T. Livinghouse, S. K. Bae, *Synthesis* **2001**, 2341-2347; (r) C. E. Headley, S. P. Marsden, *J. Org. Chem.* **2007**, *72*, 7185-7189; Catalytic asymmetric synthesis: (s) C. Scriban, D. S. Glueck, *J. Am. Chem. Soc.* **2006**, *128*, 2788-2789; (t) V. S. Chan, I. C. Stewart, R. G. Bergman, F. D. Toste, *J. Am. Chem. Soc.* **2006**, *128*, 2786-2787; (u) C. Korff, G. Helmchen, *Chem. Commun.* **2004**, 530-531; (v) G. Cedric, S. J. Canipa, P. O'Brien, S. Taylor, *J. Am. Chem. Soc.* **2006**, *128*, 9336-9377; (w) V. S. Chan, R. G. Bergman, F. Toste, D., *J. Am. Chem. Soc.* **2007**, *129*, 15122-151233.

[4] For reviews of *P*-stereogenic compounds, see: (a) A. Grabulosa, J. Granell, G. Muller, *Coord. Chem. Rev.* **2007**, *251*, 25-90; (b) D. S. Glueck, *Synlett* **2007**, 2627-2634; (c) M. J. Johansson, N. C. Kann, *Mini Reviews in Organic Chemistry,* **2004**, *1*, 233-247; (d) K. M. Pietrusiewicz, M. Zablocka, *Chem. Rev.* **1994**, *94*, 1375-1411.

[5] A. Grabulosa, Ed.; *P-Stereogenic Ligands in Enantioselective Catalysis*, Royal Society of Chemistry: Cambridge, UK, **2011.**

[6] (a) E. Bergin, C. T. O'Connor, S. B. Robinson, E. M. McGarrigle, C. P. O'Mahony, D. G. Gilheany, *J. Am. Chem. Soc.* **2007**, *129*, 9566-9567; (b) K. V. Rajendran, L. Kennedy, D. G. Gilheany, *Eur. J. Org. Chem.* **2010**, 5642-5649.

[7] (a) R. Appel, M. Halstenberg, *Tertiary Phosphane Halogenoalkane Reagents*, in; *Organophosphorus Regents in Organic Synthesis,* J. I. G. Cadogan, Academic Press, London, **1979**, Chapter 9, p. 387; (b) I. M. Downie, J. B. Holmes, J. B. Lee, *Chem. Ind. (London)* **1966**, 900.

[8] (a) K. Naumann, G. Zon, K. Mislow, *J. Am. Chem. Soc.* 1969, **91**, 7012; (b) K. Naumann, G. Zon, K. Mislow, *J. Am. Chem. Soc.* 1969, **91**, 2788; (c) G. Zon; K. E. DeBruin, K. Naumann, K. Mislow, *J. Am Chem Soc.* 1969, **91**, 7023; (d) B. D. Vineyard, W. S. Knowles, M. J. Sabacky,; G. L. Bachman, D. J. Weinkauff, *J. Am. Chem. Soc.* 1977, **99**, 5946; (e) D. Jr. Valentine, J. F. Blount, K. Toth, *J. Org. Chem.* 1980, **45**, 3691; (f) L. D. Quin, K. C. Caster, J. C. Kislaus, K. A. Masch, *J. Am. Chem. Soc.* 1984, **106**, 7021; (g) T. Imamoto, S. Kikuchi, T. Miura, Y. Wada, *Org. Lett.* **2000**, *3*, 87-90.

[9] R. M. Denton, J. An, B. Adeniran, *Chem. Commun*. **2010**, *46*, 3025; R. M. Denton, J. An, B. Adeniran, A. J. Blake, W. Lewis, A. M. Poulton, *J. Org. Chem.* **2011**, *76*, 6749-6767.

---

[10] With a 3 second acquisition time.

[11] J. B. Hendrickson, M. Singer, Md. S. Hussoin, *J. Org. Chem* **1993**, *58*, 6913-6914.

[12] K. E. Elson, I. D. Jenkins, W. A. Loughlin, *Org. Biomol. Chem.* **2003**, *1*, 2958-2965.

[13] Any longer may lead, in some cases, to a loss in yield and enantiomeric excess.

[14] K. V. Rajendran, D. G. Gilheany, *Chem. Commun.* **2011**, *48*, 817-819.

[15] A. Staubitz, A. P. M. Robertson, M. E. Sloan, I. Manners, *Chem. Rev.* **2010,** 110, 4023-4078.